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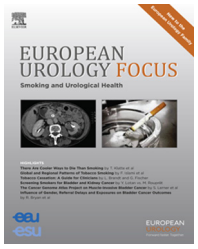

Review – Prostate Cancer

Inflammation, Microbiota, and Prostate Cancer

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Article info

Article history:
Accepted August 18, 2016

Associate Editor:
James Catto

Keywords:
Inflammation
Microbiota

Abstract

Context: Chronic inflammation of the prostate has been associated with preneoplastic lesions and cancer development. Multiple causes have been considered for chronic inflammation of the prostate. Inflammatory cytokines such as interleukins are implicated in prostate carcinogenesis and development.
Objective: To evaluate literature published on etiological factors, urinary microbiota, morphological features of proliferative inflammatory atrophy and high-grade prostate intraepithelial neoplasia, genetic polymorphisms, inflammatory stress, and cytokine signaling.
Evidence acquisition: We searched literature from PubMed from 2010 and also included the most important publications from the previous period.
Evidence synthesis: Prostate cancer inflammation and premalignant lesions have been frequently discussed in scientific literature. A limited number of models are available for studying inflammation and premalignant lesions. However, morphological pathology could be complemented by analysis of gene polymorphisms in these patients and appropriate functional studies.
Conclusions: Prostatitis could be caused by bacterial or viral infections, dietary compounds, and changes in testosterone:estradiol ratio. In some cases, the microbiota can exert direct effects on cancer development. Prostate inflammatory atrophy or high grade prostate intraepithelial neoplasia have been associated with response to cellular stress and have been discussed in connection to early cancer development. A large number of genetic polymorphisms have been identified in inflammatory prostate. Genetic and epigenetic alterations may be a consequence of the proinflammatory stress in the prostate. Proinflammatory cytokines interleukin-6 and -8 contribute to prostate malignancy; however, their function was more frequently investigated in cancer tissue rather than in inflammation.
Patient summary: We performed a review of recent literature related to prostate inflammation, microbiota, and prostate cancer. New functional approaches are required for a better understanding of the role of inflammation and cancer development.

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http://dx.doi.org/10.1016/j.euf.2016.08.010
2405-4569/

1. Introduction

Changes in prostate cancer (PCa) incidence and mortality could be attributed to improved diagnostics and therapeutic procedures during the last decade in Europe and USA. The focus on early PCa detection which included increased efforts to diagnose small prostate tumors resulted in advanced diagnostics and an increased number of successful interventions (ie, radical prostatectomies and radiation therapy). However, many of these treated cancers would have never progressed to a clinically manifested disease. Therefore, *active surveillance* has emerged as an important clinical management option during the last decade for this specific PCa patient subgroup.

Despite great worldwide efforts to find new treatment strategies to treat PCa, the disease is still incurable in advanced stages. For this reason, it is important to improve our understanding of PCa development and progression, including premalignant lesions. We will therefore specifically focus in this review on the role of inflammation, exogenous and endogenous factors such as the microbiota, and changes in gene expression during the development and progression of PCa.

2. Evidence acquisition

2.1. Etiological factors contributing to chronic prostatic inflammation

Several etiological factors are proposed to contribute to the development of prostate inflammation: bacterial and viral infections, dietary carcinogenic compounds, alterations in testosterone to estradiol ratio, physical trauma caused by the presence of corpora amylacea and prostatic calculi, and urine reflux [1]. Prostatitis could be classified, according to the National Institutes of Health as: (1) acute bacterial prostatitis, (2) chronic bacterial prostatitis, (3) chronic nonbacterial prostatitis, and (4) asymptomatic inflammatory prostatitis. Interestingly, a study found a higher incidence of inflammation in the African-American population compared with the European-American [2]. These findings are of considerable interest because of the well-known aggressive clinical course of PCa in the African-American population.

Geographic differences in the incidence and clinical behavior of PCa are well known. This malignancy is less frequent in the Southeast and East Asian population. Inhabitants of many countries in Asia consume low amounts of food rich in heterocyclic amines, which are generated in meats cooked at high temperatures and are known to induce premalignant lesions and PCa in experimental in-vivo studies in Fisher 344 rats. Of interest, Borowsky and colleagues [3] observed inflammatory infiltrates and atrophy prior to the development of prostatic intraepithelial neoplasia (PIN) in rats consuming 2-amino-1-methyl-6-phenylimidazo 4 5-b pyridine (PhIP) and Nakai and colleagues [4] demonstrated a PhIP-induced increase in the number of stromal mast cells and macrophages in the ventral lobe of the rat prostate (the only lobe that develops PhIP-induced precursor lesions) that did not occur in the other prostatic lobes. Furthermore, Sfanos et al [5] demonstrated that stromal mast cell numbers remain elevated in the ventral lobe of the prostate for many weeks following PhIP exposure. Collectively, these studies provide some clues as to an inflammation-mediated mechanism by which consumption of meat cooked at high temperatures may contribute to prostate carcinogenesis. They contribute to the understanding of geographic differences in the incidence of PCa since dietary habits considerably vary between the populations.

In addition to heterocyclic amines, cigarettes containing n-6 fatty acids, to which linoleic acid belongs, should be considered a causative factor in oxidative stress and inflammation. In contrast, reduced PCa risk was reported for individuals who regularly use nonsteroidal anti-inflammatory drugs. However, the magnitude of this effect is a subject of investigation [6]. Nonsteroidal anti-inflammatory drugs are known to target cyclooxygenase-2, an enzyme that is increased in proliferative inflammatory atrophy (PIA), although the consistency of its expression in PCa is still somewhat controversial since some studies indicate a common upregulation, yet others do not. A statistically significant 16.3% reduction in PCa risk was observed in men who used aspirin over a long-term period.

Finally, corpora amylacea and to a lesser extent prostatic calculi are frequently observed in the prostate of adult men [7,8]. They are composed of proteins that are characteristically involved in inflammation and specifically in neutrophil granules, such as lactoferrin, calprotectin, and defensins. It has been hypothesized that the presence of corpora amylacea represent evidence of past bacterial infections and inflammatory events in the prostate [8].

2.2. The urinary tract microbiome and prostate inflammation

It is well known that prostatitis can be frequently caused by species such as *Escherichia coli* and *Enterococcus* species [9]. With regard to the relative risk of men with prostatitis to develop PCa, no definitive conclusion has been reached to date. This issue will remain an area of future research. It has been demonstrated, however, that prostatic inflammation induced by prostate infections with uropathogenic *E. coli* and other proinflammatory species such as *Propionibacterium acnes* may induce morphological alterations (sometimes referred to as dysplasia) and hyperplasia, a fact which should be considered in studies on carcinogenesis. These changes have been associated with decreased expression of the tumor suppressor NKX 3.1 in the prostate [10]. A more detailed overview with regard to the contribution of other bacterial strains to inflammatory processes in the prostate is provided in reviews by Sfanos and de Marzo [11]. Clinically, acute prostatitis is characterized by a transient elevation of prostate-specific antigen expression [12], and there is a series of studies by Sutcliffe et al [13] that show prostate-specific antigen elevation during infection with common sexually transmitted infections (STIs), indicating possible prostate involvement in some instances of these infections. Men with a history of

Please cite this article in press as: Puhr M, et al. Inflammation, Microbiota, and Prostate Cancer. Eur Urol Focus (2016), http://dx.doi.org/10.1016/j.euf.2016.08.010